



Methadone ameliorates multiple-low-dose streptozotocin-induced type 1 diabetes in mice

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ABSTRACT

Type 1 diabetes is an autoimmune disease characterized by inflammation of pancreatic islets and destruction of β cells by the immune system. Opioids have been shown to modulate a number of immune functions, including T helper 1 (Th1) and T helper 2 (Th2) cytokines. The immunosuppressive effect of long-term administration of opioids has been demonstrated both in animal models and humans. The aim of this study was to determine the effect of methadone, a μ -opioid receptor agonist, on type 1 diabetes. Administration of multiple low doses of streptozotocin (STZ) (MLDS) (40mg/kg intraperitoneally for 5 consecutive days) to mice resulted in autoimmune diabetes. Mice were treated with methadone (10mg/kg/day subcutaneously) for 24 days. Blood glucose, insulin and pancreatic cytokine levels were measured. Chronic methadone treatment significantly reduced hyperglycemia and incidence of diabetes, and restored pancreatic insulin secretion in the MLDS model. The protective effect of methadone can be overcome by pretreatment with naltrexone, an opioid receptor antagonist. Also, methadone treatment decreased the proinflammatory Th1 cytokines [interleukin (IL)-1 β , tumor necrosis factor- α and interferon- γ] and increased anti-inflammatory Th2 cytokines (IL-4 and IL-10). Histopathological observations indicated that STZ-mediated destruction of β cells was attenuated by methadone treatment. It seems that methadone as an opioid agonist may have a protective effect against destruction of β cells and insulinitis in the MLDS model of type 1 diabetes.

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Introduction

Insulin-dependent diabetes mellitus (IDDM) is an autoimmune disease. Type 1 diabetes results from specific destruction of the insulin-producing β -cells in the pancreatic islets of Langerhans by the immune system (Bach, 1994). It is believed that destruction of pancreatic islet β cells and consequent IDDM is the result of perturbed immune regulation. Multiple environmental and genetic factors make the immune cells, particularly T lymphocytes to invade islet β cells and cause pancreatic inflammation (Rabinovitch and Suarez-Pinzon, 1998). This inflammatory response is known as insulinitis (Pukel et al., 1988). Cytotoxicity of T cells towards islet β cells is generated by cytokines and free radicals. Autoreactive T helper 1 (Th1) cells and proinflammatory cytokines [interferon (IFN)- γ , interleukin (IL)-1 and tumor necrosis factor (TNF)- α] are pathogenic to islet β cells, whereas T helper 2 (Th2) cells and their cytokines (IL-4 and IL-10) are protective against destruction of β cells (Rabinovitch, 1998). Blocking the function of type 1 cytokines and increasing type 2 cytokines can

reduce the development of IDDM in rodent models (Rabinovitch and Suarez-Pinzon, 1998).

Multiple low doses of streptozotocin (STZ) (MLDS) can be used as an animal model for type 1 diabetes. STZ is a potent alkylating agent and damages islet β cells selectively by two different mechanisms. First, when given in a single high dose, it rapidly destroys islet β cells by direct cytotoxic action, most probably due to DNA alkylation. Second, when STZ is given in multiple low doses, it induces inflammation of the islets by immune cells, with subsequent destruction of β cells and progressive hyperglycemia within a few days. This model of diabetes shares many histological and clinical features with human type 1 diabetes and requires the participation of macrophages and T cells (Like and Rossini, 1976; Rossini et al., 1978; Papaccio et al., 2000). Therefore, the MLDS model has been applied extensively to study the immune pathways (e.g. cytokine signaling, Fas ligand transduction and cytokine-induced β cell apoptosis) involved in destruction of islet β cells (Kawasaki et al., 2004; Rees and Alcolado, 2005).

It is believed that the endogenous opioid system regulates immune functions. Previous studies have established the presence of opioid receptors (μ , κ and δ) on cells of the immune system (Mehriishi and Mills, 1983). Many animal and human studies have shown that opioids induce immunosuppressive effects, and chronic opioid use has been associated with an increased incidence of infection (Budd, 2006).

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